

SCHOOL OF MEDICINE  
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Dear Frank:

I have been mulling over some of the issues posed by your manuscript on heterologous integration and the reviewers' remarks for several weeks. I am sorry I have not had very much time to devote to this on account of other trips but there may be some merit to a brief delay if it has given you time to think over the basic issues.

I have decided to communicate the paper to the Proceedings since it obviously contains a contribution of extraordinary interest and importance, despite some reservations that I am sure you share. Some of the remarks could be set aside as quibbles if there were a clear demonstration that a hybrid chromosome had in fact been achieved. The proposed mechanism of integration is entirely plausible but obviously *it* will take a great deal of further effort to nail down with any conclusiveness and I suspect that it is the empirical finding that you yourself would want to emphasize as your contribution.

I guess that none of <sup>us</sup> ~~this~~ is really deeply impressed with the evidence of integration into the chromosome. One way to look at it is to ask what would your degree of astonishment be if you had to reconcile the data that you presented with other information that the plasmid was indeed replicating independently? You are pinning a lot on the chemical identity of high molecular weight DNA as containing segments homologous to the plasmid since you don't give any details, and probably don't really know, whether that preparation contains anything other than covalent phosphodiester linkages. Have you looked around at other restriction enzymes to see if you could isolate well-defined segments that would nail down the chimeric structure?

Alternatively, if you have made some further headway with using the chimeric chromosome "to recombine other pMB9 chimeric plasmids" that should be able to lead to a fairly early resolution of the story, for example by linkage studies involving both subtilis and coli markers.

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My own predilection would have been to wait, before publishing the article, for more rigorous evidence on the integration into the chromosome; but that is a judgment I feel you must make and hindsight has shown that I was not always wise to wait to plug every loophole.

Although the paper is on the way to the Proceedings as I believe you would wish you would still have ample time to call them up if you now preferred to intervene, for example, to include more recent data.

Let none of the above obscure the very high importance of this finding, the likelihood that you are right in your interpretation, and the fact that I wish we had been the ones to get there first! We were, of course, looking very hard for such a phenomenon and I am still puzzled about the real reasons that enabled <sup>me</sup> to see it in your system and why it has not been picked up with the pSC101 hybrid plasmids. Perhaps it is just that we did not look hard enough and should sometime go back to that.

Yours sincerely,

Joshua Lederberg,  
Professor and Chairman,  
Department of Genetics

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